Agent Based Modeling of Neurovascular Unit Development

Todd J. Zurlinden, Katerine S. Saili, Thomas B. Knudsen

National Center for Computational Toxicology
Office of Research and Development
Research Triangle Park, NC

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This work does not necessarily reflect EPA policy
U.S. Environmental Protection Agency
• **Problem:** Multiscale modeling approach will improve toxicity predictions for chemicals from organotypic culture models

• **Hypothesis:** Use of computer models that recapitulate morphogenesis will improve analytically and theoretically based predictions of developmental toxicity.

• **Integration:** A model system which recapitulates the biology, and leverages both knowledge of cell-cell interactions and the available high-throughput *in vitro* profiling data
Computational neurovascular unit (cNVU) focus

- Vascularization of the neuroepithelium results from angiogenesis.
  - Sprouting from the perineural vascular plexus.

- Microglia, resident macrophages of the brain, meditate neurogenic and angiogenic signaling.
  - Are they mediators of developmental toxicity?

- A cellular-dynamic computational systems model of microglial function can improve our ability to understand and predict NVU DevTox.

Agent-Based Modeling and Simulation (ABMS): a heuristic approach to reconstruct tissue dynamics using knowledge of biochemistry and cell-by-cell interactions.

- Program each agent (cell) to follow specific rules
- Interactions of agents gives rise to emergent features (phenotypic outcomes)
- Qualify emergent feature with experimentally derived phenotypes (tissue level morphology)
- Make toxicodynamic predictions by integrating biological knowledge & high throughput data

CompuCell3D*: open source modeling environment

- Rules (steppables) for distinct cell behaviors (growth, proliferation, apoptosis, differentiation, polarization, motility, ECM, signal secretion, …);
- Rules coded in Python for cell-autonomous ‘agents’ that interact in shared microenvironment and self-organize into emergent phenotypes.

*James Glazier and colleagues, Indiana University
• **Goal**: build a cellular ABM that simulates microglia-mediated angiogenesis and neurogenesis.

• **Simulate**: exposure to ToxCast chemicals predicted to be neurovascular disruptors
  - Data from neurogenesis (ArunA) and angiogenesis (Vala)

• **Qualify**: simulation outputs against cell-based angiogenic and neurogenic assays.
  - proliferation, migration, tubulogenesis, branching, etc.
Cell-signaling network

Stalk Cell

Tip Cell

NICD

dll4

notch

NICD

dll4

vegfr3

vegfr2

CSF1

Migration (ventricle)

Anastomoses

VEGF-C

Microglia

NICD < Threshold

Tip Cell

Neuroepithelium

VEGF-A

cs1r
1. Vessel Stabilization

- Neuroepithelium
- Stalk Cell
- Tip Cell
- dll4
- notch
- NICD
- VEGF-A
- vegfr2
- vegfr3
- CSF1
- cs1r
- VEGF-C
- Migration (ventricle)
- Anastomoses

NICD < Threshold Tip Cell
1. Vessel Stabilization

Neuroepithelium

Tip Cell

NICD < Threshold

Tip Cell

dll4

notch

vegfr2

CSF1

vegfr3

NICD

tomoses

VEGF-A

 dll4

notch

NICD
2. Microglia Anastomosis

- Neuroepithelium

- Stalk Cell
  - dll4
  - NICD
  - notch

- Tip Cell
  - dll4
  - notch
  - NICD
  - vegfr2
  - vegfr3
  - CSF1

- Migration (ventricle)
- Anastomosis
  - CSF1
  - vegfr3
  - dll4
  - notch
  - NICD < Threshold
  - Tip Cell
  - VEGF-C
  - Microglia
cNVU boundary conditions

VEGF-A (NPC gradient)

Perineural Plexus
Neuroepithelium
Ventricular Surface

Tata et al., PNAS, 2016
Vascularization without microglia

Perineural Plexus

Neuroepithelium

Ventricular Surface
Embryonic vasculature
Toxicity-specific predictions

• Utilize concentration-response assays for Csf1r in ToxCast
  – Csf1r inhibition tied directly to microglia abundance (growth/survival)
  – *in vivo* studies demonstrate a decrease in vascular branching in the absence of microglia.

Rymo et al., PLoS one, 2011

Csf1<sup>op/op</sup>: microglia “knockout”

mouse retina
Quantitative response: microglia abundance

2x 1.5x 1x (prototype) 0.8x

0.6x 0.4x 0.2x 0x
Towards a functional cNVU model

• Preliminary description of the role of microglial-endothelial interactions

• Next steps – include more cell types and features to better recapitulate NVU development
  – Capture neuroprogenitor cell NVU contribution
  – Incorporate 3D dynamics and vascular flow
  – Integrate available biological knowledge with HTS ToxCast data to simulate NVU developmental processes and toxicities

Brown et al., *Biomicrofluidics*. 2013
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Questions?